

**REMARKS**Rejection Under 35 U.S.C. § 102(b)

Claims 1, 4, 5, 7, 9 and 10 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent 5,547,669. Of these claims, claim 1 is the sole independent claim, the remaining claims of this group being dependent directly or indirectly from claim 1. Claim 1 has been amended to state that the linker peptide comprises nine or more amino acid residues. Support for this amendment is found on page 7, lines 27 and 31, which show two linker peptides of nine amino acid residues. It is urged that the limitation that the linker peptide comprise at least nine amino acid residues distinguishes the claims from the '669 patent disclosure. The '669 patent teaches use of peptide linkers which are charged amino acid pairs such as KK or RR (see column 15, lines 59-60). These amino acid pairs of the '669 patent are inserted to give protease sensitive sites. The linkers of the present application have a different purpose and need to be longer than two amino acid residues. The linkers of the present application are present to allow each of the separate peptides to be independent of each other so that they retain their normal conformation, thereby retaining the ability of autoantigens to recognize each peptide. This is explained on page 12, lines 9-12, of the present application. Furthermore, these linkers can be labeled with biotin or other similar agent rather than having the epitopes of PPINS, GAD65 or IA2 heavily labeled with biotin. This allows the epitopes to remain available for binding to autoantibodies rather than being blocked by the biotin. This is explained, e.g., on page 6, lines 19-26, and page 12, lines 15-21. These nine or longer amino acid residue linkers therefore serve completely different purposes than do the short, two amino acid residue linkers of the '669 patent. Furthermore, they are physically very different (9 or more residues vs. 2 residues). It is urged that this difference is neither anticipated by nor made obvious by the '669 patent.

In view of the amendment to the claims and the above comments, it is requested that the rejection under 35 U.S.C. § 102(b) be withdrawn.

The 35 U.S.C. § 103(a) Rejections

Claims 1-5, 7-10 and 17 were rejected under 35 U.S.C. § 103(a) as being obvious over Rogers et al. (U.S. Patent 5,547,669) in view of Rabin et al. (U.S. Patent No. 5,200,318), Maclaren et al. (U.S. Patent 5,989,551), Hummel et al. and Berg et al. In this group of claims, only claim 1 is an independent claim, the remaining claims depending directly or indirectly from claim 1. As discussed above, claim 1 has been amended to require the linker protein to comprise nine or more amino acid residues. It is urged that none of the cited references teaches such linker peptides. The Berg et al. reference teaches inclusion of a six amino acid histidine sequence, but this six amino acid sequence is neither nine or more amino acid residues and also is not a linker peptide, rather it is near the amino terminus of a protein and is not used to link different epitopes.

In view of the amendment to the claims, it is urged that the claims are not made obvious by the cited references and it is requested that the rejection of claims 1-5, 7-10 and 17 under 35 U.S.C. § 103(a) be withdrawn.

Claims 1-10 and 17-18 were rejected under 35 U.S.C. 103(a) as obvious over Rogers et al., in view of Rabin et al., Maclaren et al., Hummel et al., Berg et al., and WO 94/07464. Claims 1 and 18 are the sole independent claims of this group and both of these claims have been amended to require that the linker peptide comprise nine or more amino acid residues. The only difference between this rejection and that described above is the inclusion of WO 94/07464 as a teaching of biotin or streptavidin as part of the fusion protein which is a limitation of claim 6. As discussed just above, the amended claims require a linker peptide comprising nine or more amino acid residues. The WO 94/07464 reference was cited only for a teaching of biotin and streptavidin and does not address the issue of a linker peptide of nine or more amino acid residues. In view of the amendments to the claims and the above comments, it is urged that claims 1-10 and 17-18 are not made obvious by the cited references and it is requested that this rejection be withdrawn.

Claims 1-5, 7-10 and 17-20 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Rogers et al. in view of Rabin et al., Maclaren et al., Hummel et al., Berg et al., and Xu et al. or Hemmila et al. The difference between this rejection and the preceding rejections is the citation of the Xu et al. and Hemmila et al. references. These were cited to teach a label which is radioactive, fluorescent or a lanthanide. Once again, the claims have been amended such that they all require the presence of a linker protein comprising nine or more amino acid residues. Neither the Xu et al. nor Hemmila et al. reference teaches this limitation. In view of the amendments to the claims and the above comments, it is urged that the cited references do not make the claims obvious and it is requested that the rejection be withdrawn.

#### The Newly Added Claims

Claim 21-28 are added by this Amendment. These claims depend from claim 1 or claim 18 and all include the limitation that the peptide linker comprise nine or more amino acid residues. All of these being dependent claims, they incorporate other limitations in addition to those of claims 1 and 18. Claims 21 and 25 require that six or more of the amino acid residues of the linker be lysine. Support for this is found on page 7, lines 27 and 31, where two such linkers are set forth. These two linkers are the subject matter of claims 22 and 26. The purpose of the lysines is that they compete for biotin under limiting biotin supply thus leaving the important lysines in the potential antigenic epitopes of the peptides free for binding.

The limitations of claims 23-24 and 27-28 are the requirement that the linker be labeled with a member of an affinity binding pair and that this can be a biotin-streptavidin binding pair. Support for these limitations can be found at page 6, lines 19-22, and also in originally filed claims 5 and 6.

In view of the amendments and the above arguments, it is submitted that the present claims satisfy the provisions of the patent statutes and are patentable over the prior art. Reconsideration of this application and early notice of allowance are requested.

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**Attachments:** Marked-Up Copies of Amendment to Claims 1, 7 and 18.

**Amended Claims 1, 7 and 18: Version with markings to show changes made**

--1 (three times amended). A fusion protein presenting epitopes of at least two autoantigens wherein [one of said autoantigens is preproinsulin (PPINS) and a second of] said autoantigens [is] are selected from the group consisting of: preproinsulin (PPINS), glutamic acid decarboxylase (GAD65) and islet cell antigen (IA2), wherein said epitopes are connected with a linker peptide, wherein said linker peptide comprises nine or more amino acid residues, said fusion protein being able to bind to a solid phase.--

--7 (twice amended). A cDNA encoding the fusion protein according to claim 1 wherein said cDNA comprises nucleotide sequences encoding epitopes of at least two autoantigens wherein [one of said autoantigens is preproinsulin and a second of] said autoantigens [is] are selected from the group consisting of: preproinsulin (PPINS), glutamic acid decarboxylase (GAD65) and islet cell antigen (IA2).--

--18 (amended). A fusion protein presenting epitopes of at least two autoantigens selected from the group consisting of glutamic acid decarboxylase, islet cell antigen and preproinsulin, wherein said fusion protein comprises a label and a linker peptide wherein said linker peptide comprises nine or more amino acid residues.--